IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Applicant: Karel Newman, *et al.*

Art Unit 1806

Serial No.: 08/070,099

Atty. Docket No. 19867.1.0

Filed: 05/28/93

For: IMMUNOASSAYS FOR DETERMINING VITAMIN B12 AND REAGENTS AND KITS THEREFOR

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Attention: Board of Patent Appeals and Interferences

APPELLANT'S REPLY BRIEF (37 CFR 1.193(b))

An Amended Appellant's Brief was filed July 20, 1995 in this Appeal. The Examiner's Answer was mailed November 29, 1995, raising new grounds of rejection. The period for filing this Reply Brief in response to those new grounds of rejection is set to expire January 29, 1996.

Appellants have provided a proposed Amendment below. Entry of this Amendment is within the discretion of the Examiner and is respectfully requested. In the event the Examiner is inclined to deny entry of the Amendment, either the Examiner or the Board are encouraged to exercise the discretion accorded them in reopening prosecution of this

application, in order to enter the Amendment and fully and fairly consider the issues involved.

In the event any fees are in order in connection with this Reply Brief, authorization is hereby provided to debit Deposit Account No. 06-1910.

In the Claims

Kindly amend the claims as follows:

Claim 8, delete "8" and insert therefor -- 7 --.

Claim 9, after "in the presence" insert -- of vitamin B12 --.

Remarks

This Reply Brief will address the new grounds of rejection by reference to the headings provided in the Examiner's Answer.

I. STATUS OF CLAIMS - confirmed

II. STATUS OF AMENDMENTS - confirmed

III. SUMMARY OF INVENTION - confirmed

IV. ISSUES

In view of the Examiner's Answer, the grouping of rejections is as follows:

A. **Rejections Withdrawn**

1. The rejection of claims 2-8 under Section 103 in view of Chen and Galfre.

2. The rejection of claims 9-10 under Section 103 in view of Chen.

B. **Rejections/Objections Maintained**

1. The objection to the specification, and related rejection of claims 1-10 under Section 112, first paragraph.

2. The rejection of claim 1 under Section 102(b) over Smolka *et al.*

C. **New Grounds of Rejection**

1. The rejection of claims 2-6, 9 and 10 under Section 103 over Smolka *et al.* in view of Ellis *et al.*

2. The rejection of claims 7 and 8 under Section 103 over Smolka *et al.* in view of Galfre.

3. The rejection of claims 9 and 10 under Section 112, second paragraph.

V. GROUPING OF CLAIMS

Response to the Examiner's concerns under this section is essential for a complete response to the new grounds of rejection. It may be recalled that Appellants' Amended Brief confirmed that the claims will stand or fall together. This statement was made solely to facilitate resolution of this appeal, and was not intended, nor is it properly construed, to imply that there are not different issues or grounds of rejection involved. To the contrary, each ground of rejection was recognized and addressed in Appellant's Amended Brief.

As set forth in MPEP Section 1206, the statement made by Appellants merely confirms that "for *each ground* of rejection which appellant contests, and which applies to a group of two or more claims" (emphasis added), it is the *broadest* claim in each group that will be considered for the purposes of patentability.

The Examiner appears to concur with this approach, for instance, as seen in the introductory comments made at page 9 regarding the new grounds of rejection, which state: "the point of patentability in the instant methods of diagnosis and kits for use therewith is essentially the antibody".

On the other hand, at paragraph (11), page 11, the Examiner further states that Appellants "argue essentially" that "all grounds of rejection will fall" upon resolution of the experimental data. This is simply not the case. What Appellants *do* propose is that discussions of the prior art, and of support in the specification, have both become mired in disagreement generated by the Examiner's concerns regarding the experimental data.

In reviewing the new grounds of rejection (including their incorporation and reliance on the Section 102 rejection being maintained), one can distill three common and recurring issues that provide a framework for their analysis. In order for these grounds to be fully explored, let alone resolved, these issues are preferably addressed in order. They include:

(a) An understanding of Appellants' definition of the term "allosteric competitive";

(b) The interpretation of the data, and in particular, the extent to which it supports that definition; and finally,

(c) Patentability of the claims, as defined, including the extent to which they distinguish over the art of record, and the extent to which they are adequately supported and enabled by the specification.

It will be seen that Appellants have two hurdles to overcome, in addition to meeting the usual requirements for patentability. They need to describe an antibody having novel characteristics that are unlike most others, and they need to do so based on the results of an

analytical technique that is itself relatively new to the industry. It may help to recall that the relationship between intrinsic factor, vitamin B12, and their uptake in the GI tract is itself unique. Only then, and with a proper framework in mind, can these hurdles be fairly addressed and overcome.

VI. CLAIMS APPEALED

Claim 8 has been amended by recasting it as dependent on claim 7, thereby confirming the Examiner's interpretation. Claim 9 has also been editorially amended, in the manner described below with respect to the new ground of rejection under Section 112. Accordingly, upon entry of this Amendment, the claims on appeal are confirmed.

VII. PRIOR ART OF RECORD - confirmed

VIII. ARGUMENTS - The new grounds of rejection will be addressed in the order in which they appear, using the analytical framework set forth above.

1. **The rejection of claims 2-6, 9 and 10 under Section 103 over Smolka *et al.* in view of Ellis *et al.* is respectfully traversed.**

(a) Definition of "allosteric competitive".

Appellants have provided a two-part definition of the phrase "allosteric competitive" as applied to their antibodies. That definition provides, in effect, that the antibody is able to bind to intrinsic factor ("IF") *only* in the absence of B12, *and that if previously bound*, the

antibody can be "bumped" from its bound position upon the addition of B12. It is the unique combination of both attributes that provides the patentable invention.

In the new grounds of rejection the Examiner focuses only on the former attribute, or at best vacillates between the two individually. At page 3 of the Answer, for instance, the Examiner misinterprets, or mischaracterizes, Appellants' specification as describing antibodies that are competitive "in the 'allosteric' sense in that the antibodies cannot be bound to intrinsic factor at the same time vitamin B12 is bound to intrinsic factor."

Again at page 8, with reference to Smolka *et al.*, the Answer concludes "[s]ince Smolka teaches a [*sic*] antibodies having a binding activity where the antibody can only bind intrinsic factor in the absence of B12, the claims are anticipated." Yet again, at the last lines of page 15, the Examiner concludes that the "function" of the antibodies in both Smolka *et al.* and the present invention is merely "the ability to interrupt or compete for the binding of IF with B12".

As a result, the Examiner continues to insist that the present antibody is one that binds at the B12 binding site, *and* that it does so in a conventional competitive manner with B12 (see, e.g., page 4, line 8 and page 1, lines 1-16). The data, however, shows that both of these assertions must be incorrect. Instead, the data supports the conclusion that the present antibody binds to a site on IF that is distinct from the B12 site *and* that it does so in a manner that causes it to become disassociated upon the binding of B12.

To focus on but a single attribute while ignoring the other, or their combination, is both unfair to Appellants and confusing to the Board, and is akin to identifying only one element in an alloy. The Examiner has failed to identify anything in either Smolka *et al.* or

Ellis *et al.*, either alone or combined, that teaches or suggests an antibody having *both* characteristics of the combination presently claimed.

(b) Interpretation of the data

The Examiner remains unwilling to accept the interpretation of the data set forth by Appellants. This unwillingness, however, is based more upon the Examiner's inability to accept the definition of "allosteric competitive" than it is upon an alternative interpretation. The Examiner's comments regarding Appellants' Figure 1, for instance, are generally not disputed. The protocol and related results of Figure 1 *do* appear to indicate a conventional competitive situation.

It is the results of the BIAcore (biospecific interaction analysis) method, however, that lead Appellants to the present invention. These results, including Figure 2 itself, were specifically added in the course of re-filing this application as a CIP. By failing to distinguish between allosteric and conventional forms of competition, the Examiner also fails to distinguish between the teachings of the respective figures.

Without the particular screening and other techniques taught by Appellants, and in particular the recent availability of BIAcore techniques, the unique properties of the present invention would likely not have been discovered. Now that these properties have been discovered, however, given the present teaching those skilled in the art will be readily able to find more such antibodies.

The BIAcore method is admittedly a new one, requiring new interpretive skills and understanding. The method was considered significant enough for the publishers to recently dedicate a 184 page "special issue" of the Journal of Immunological Methods (Volume 183,

no. 1, 1995) to the very subject. Once understood, this data ought not lead one to conclude that such an assay "contradicts the basic laws of thermodynamics".

A copy of the Preface to the special issue is enclosed for the convenience of the Examiner and the Board. As can be seen, the Preface itself is effusive in its praise of this new technology, stating that the method "represents the first time that a major methodological innovation has focussed on the determination of biological *activity* instead of biological structure" (emphasis added). It goes on to state that the technique "allows binding interactions to be measured with unparalled ease, precision, and reproducibility" and that "no other single technique can provide so much quantitative information as quickly and reproducibly".

The Board is referred to either the specification, Appellants' Amended Brief, or the special journal issue identified above for a complete description of this method. Briefly put, the technique can be used to measure the optical effects of proteins bound to the surface of a biosensor chip within a flow cell. Only those proteins (or complexes thereof) that are of sufficient size and *actually bound* to the chip will be detectable. This method was found particularly useful by Appellants, by virtue of the fact that vitamin B12 is itself too small to affect the signal. The experiment was designed, therefore, to take advantage of the fact that only antibodies and/or IF (or complexes including either or both) are large enough to be detected, if bound to the chip.

The details of the BIAcore technique have been summarized previously. In essence, the experiment leading to the results in Figure 2 involved first immobilizing allosteric competitive antibody within the cell. Intrinsic factor was then introduced into the cell, where

it was able to bind to the antibody to form a bound complex. In view of the inherent experimental design, *any unbound IF* was then washed away by the flow within the cell, and a baseline signal was generated. Although the Examiner's analysis of the method overlooks this critical aspect, it is nevertheless essential to a clear understanding of the data.

Vitamin B12 was then introduced into the cell in increasing concentrations (in separate cycles, after the regeneration of the antibody-IF surface) corresponding to the plots from the top to bottom of Figure 2. In view of the continual flow of buffer through the cell, and the binding relationships established, *only immobilized complexes (i.e., antibody/IF or antibody/IF/B12)* were detectable. Any component that was not present in immobilized form would be washed from the cell, and hence not detected.

The data in Figure 2 clearly shows that with each increase in B12 concentration, the detectable signal ("relative response") decreased over time. The Examiner's concerns regarding the labelling of this Figure are unfounded and confusing. The plot of Figure 2 sets forth a response that is made "relative" solely in order to align each plot with time zero. Moreover, the Examiner's statement to the effect that the "X axis does not show time, it show "seconds in dissociation phase" is inconsistent and falls of its own weight. The plot of Figure 2 is clearly a proper, conventional, and helpful one for understanding the results of the BIAcore technique.

It can be seen in Figure 2 that the amount of immobilized IF decreased with increasing B12 concentrations. Under the conditions of this BIAcore experiment, these results *can only mean* that the antibody/IF complex was becoming disassociated (that is, IF

became unbound) at an increasing rate with increasing B12 concentration, as compared to the control rate established at 0 micromolar B12.

The comments in the Examiner's Answer make it apparent that the Examiner fails to appreciate the experimental protocol, and in turn the data. Moreover, the Examiner also mischaracterizes Appellants' conclusions regarding the data. At page 4, for instance, she asserts that Appellants conclude that a "dynamic equilibrium" exists. If anything can be distilled from the above explanation of this technique (and in particular the manner in which unbound reagents are continually removed from the cell), it is that no such equilibrium is established - dynamic or otherwise.

The antibody of the present invention can only be "allosteric competitive", in the manner defined by Applicants, since it is capable of specifically binding to IF only in the absence of B12 (as seen in Figure 1) *and* is released from binding in the presence of B12, and upon the binding of B12 to IF (as seen in Figure 2).

The Examiner maintains that the data is consistent with an antibody that is competitive in the *conventional* sense. If that were true, however, one would not expect to see a change in the rate of IF disassociation at increasing concentrations of B12. Rather, the common binding site on IF would initially be inaccessible to B12, since it would be in a position bound to the immobilized antibody. The IF site would only become accessible at the rate of spontaneous disassociation of IF from antibody. Once disassociated, however, any resulting IF/B12 complex would then be washed from the cell undetected, and with no effect on the overall spontaneous disassociation of remaining immobilized complexes.

An antibody that is competitive in the classic sense would also be expected to compete for binding to the same site on IF that B12 binds. In contrast, it can only be concluded that the allosteric competitive antibody of the present invention binds instead to a different site on IF, thereby providing the basis for its allosteric competitive effect of B12 on previously bound antibody.

It may well be argued that the present invention would not have been made were it not for the availability of this new and exciting analytical method. That alone, however, is no reason to prevent the grant of a patent to an invention so discovered. Nor is the newness of the method a reason to obfuscate or deny the meaning of its data.

(c) Patentability - the teachings of Smolka *et al.* and Ellis *et al.*

Smolka *et al.* merely describe how to obtain monoclonal antibodies to IF. The reference does not describe, or suggest, the selection or production of allosteric competitive antibodies as presently *defined and* claimed. Similarly, Smolka *et al.* do not describe a screening method that involves extracting B12 from culture supernatant before selecting hybridomas that secrete antibodies to IF.

In fact, the antibodies of the present invention and those of Smolka *et al.* are prepared by respective methods that would serve to exclude each other's antibodies. Applicants select antibodies that will bind only in the *absence* of B12 or IF/B12 complex (see, page 14, line 18 to page 15, line 7). Smolka *et al.* on the other hand, specifically *selects for* those that bind to the IF/B12 complex (see page 608, col. 1).

Moreover, the Examiner picks and chooses among isolated characteristics of the various, and distinctively different, monoclonals within Smolka *et al.*, yet implies that these

characteristics each describe the same monoclonal. For instance, in referring to antibodies that "conformationally affect" binding, reference is made to antibodies 5.6 and 11.5 as identified at page 612 of Smolka *et al.*

The Examiner is incorrect in concluding (at the top of page 8) that Smolka *et al.* teach antibodies that bind IF only in the absence of B12. The fact that binding is detected by the use of radiolabeled B12 would certainly indicate that the authors would not have found any such antibodies. Moreover, the results would indicate that each antibody retains substantial binding capacity for the IF/B12 complex (see, e.g. page 609, col. 2, line 6, and Figure 1).

The Examiner's "invitation" to show by side-by-side comparison that "the prior art antibody would not inherently contain the allosteric characteristics claimed" is unrealistic and unfounded in the law. Applicants cannot be expected to prove a negative, i.e., to obtain and compare every prior art antibody described as being directly competitive in order to show that they do not function in the manner presently claimed. Rather, it can be seen that the Examiner has failed to make a *prima facie* showing that the reference suggests an antibody that meets both of the functional requirements of one that is allosterically competitive.

Ellis *et al.* is cited for its teaching of a generic method of binding antibody which blocks the binding of IF to B12, and in turn is applied to the kits and method of the invention. The reference teaches a method for the detection of "autoantibodies" made by a patient that bind to IF. By binding to IF, the autoantibodies serve to prevent the binding of B12.

The Examiner agrees that the reference fails to teach or suggest the use of an allosteric competitive antibody as described and claimed by Applicants. Instead, the Examiner asserts that Appellants' "claimed method is merely substitution of an antibody for intrinsic factor on a support". This assertion, however, is illogical.

Ellis *et al.* employ immobilized IF in an assay to detect the presence of autoimmune anti-IF antibodies in the patient's blood. To replace the immobilized IF in such an assay with immobilized antibody of the present invention would defeat the very purpose of the Ellis *et al.* reference. There is no reason to believe that an allosteric anti-IF antibody would itself detect an autoimmune anti-IF antibody, nor in turn, would it provide one with the method or kit of the present invention.

2. The rejection of claims 7 and 8 under Section 103 over Smolka *et al.* in view of Galfre is respectfully traversed.

The Examiner's Answer asserts that "it would have been prima facie obvious to apply the general technique of Galfre to the specific antibodies of Smolka". As discussed both previously and above, however, there is no teaching or suggestion in Smolka *et al.* of antibodies that one could apply the Galfre techniques to.

Galfre *et al.* merely describe general methods for the preparation of antibodies. The reference does not teach or suggest the preparation or use of allosteric competitive antibodies in the manner presently claimed.

If anything, Galfre *et al.* and Smolka *et al.*, support the patentability of this invention by undermining the assertions made by the Examiner under Section 112. References such as

these demonstrate the availability of skills, processes, and reagents available to those skilled in the art, together with the present teaching, for use in making and using antibodies as presently claimed.

The application provides additional and ample tools to enable those skilled in the art to prepare, identify and recover antibodies within the scope of the invention, and without undue experimentation. Appellants' own examples (e.g., Example 1) demonstrate the manner in which a reasonable number of fusions resulted in "several" wells demonstrating the desired activity.

Moreover, Appellants dispute the Examiner's statement at page 6, line 14 regarding the need to deposit Appellants' preferred antibody. Page 10, lines 16-21 of the instant specification make it clear that the hybridoma was deposited, and accorded accession number ATCC-HB10711. It is apparent that misconceptions such as these form a substantial basis of the Examiner's concerns regarding enablement. It remains clear, however, that those skilled in the art have been provided with ample tools to ensure their success, including the traditional methods of antibody production, as well as the unique screening method presently taught, the BIAcore technique, and the deposited cell line, all in combination with Appellants key teaching that allosterically competitive antibodies exist for intrinsic factor and can be recovered.

3. The rejection of claims 9 and 10 under Section 112, second paragraph is respectfully traversed.

This rejection is rendered moot by virtue of the above editorial amendment of claim 9, inserting the phrase "of vitamin B12" after the phrase "in the presence", thereby confirming the Examiner's interpretation.

X. SUMMARY

For the foregoing reasons, it is submitted that the Examiner's rejections of claims 1-10 were erroneous, and reversal of her decision is respectfully requested.

Respectfully submitted,

Dated: 29 JAN 1996

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